Review:
Serum C-Reactive Protein as a Marker for Wellness Assessment

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Abstract. C-reactive protein (CRP), a nonspecific inflammatory marker, is widely used to monitor treatment of cardiovascular diseases (high serum CRP levels indicate poor outcome of heart disease). A healthy lifestyle decreases serum CRP levels, while obesity, physical inactivity, and smoking increase them. CRP, a stable pentameric protein, has a half-life of 19 hr, is not subject to diurnal variation, and can serve as a marker of wellness and a candidate for future direct access testing for people monitoring their health after adopting a healthier lifestyle. The CRP level may be influenced more by lifestyle than by genetics. Monozygotic twins may not have the same CRP level; within each twin pair, the one with higher adiposity generally has a higher CRP level than the one with low adiposity. Chronic diseases generally have a lower prevalence among Asians than among Westerners. Asians also have lower CRP levels than Westerners. In large population studies, the median CRP level of Asians is only one-tenth that of Westerners. Is there a factor in the lifestyle or diet of Asians that accounts for lower CRP levels? For example, a statin inhibitor of cholesterol synthesis occurs in red yeast rice, an important component of the Asian diet. In summary, CRP is a marker for monitoring cardiovascular therapy and assessing the wellness of the general population. Through improving health and preventing disease, CRP testing may help lower a nation’s health costs.

Keywords: body mass index, C-reactive protein, wellness assessment, health screening

Introduction

The National Cancer Institute set the goals of eliminating suffering and death due to cancer by 2015 [1]. The director of the National Cancer Institute has urged all scientists to contribute in whatever way possible to achieving these goals (Medical Grand Rounds, Mayo Clinic Rochester, MN, 18 August 2004). To achieve these goals, we cannot depend on treatment alone without changing the lifestyle of the general population. For example, suffering and death from lung cancer cannot be eliminated effectively unless the general population stops smoking because most (80%-90%) lung cancer patients are smokers. Currently, lung cancer is the number one cause of cancer deaths in the United States. Similarly, the suffering from cardiovascular disease, diabetes mellitus, and obesity cannot be reduced without changes in lifestyle, diet, and physical activity. Medical and surgical treatments alone cannot achieve these goals. Disease prevention should be the primary step. What role can clinical scientists assume in maintaining the health of the general population? As laboratory professionals, we can have a substantial impact on shifting medicine from disease diagnosis to wellness assessment, thereby making health care more efficient and less costly and improving the quality of life of the general population [2]. To do this, we shall need objective markers for assessing wellness, and C-reactive protein (CRP) appears to be a good candidate.

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CRP is a nonspecific marker of inflammation; it may serve as a proxy measurement for general wellness. CRP is synthesized in response to the acute phase of a bacterial or fungal infection. Structurally, it is a symmetrical ring molecule that consists of 5 noncovalent but associated protomers. Each protomer has 2 calcium ions responsible for the specific binding of phosphochlorine. Phosphochlorine is a common constituent of many bacterial and fungal polysaccharides and most biologic cell membranes, such as the phosphochlorine residues of C (or capsular)-polysaccharide of *Streptococcus pneumoniae* [3]. The protein was designated “C-reactive” because of this reaction.

CRP may be the primary defense function of the human body. Traditionally, serum CRP levels have been measured by rate nephelometry, which has a detection limit of 6 to 10 mg/L. This is the so-called “serum CRP” test. A commercially available “high-sensitivity CRP” (hs-CRP) test is a latex particle-enhanced immunoturbidimetric assay that has a detection limit of about 0.15 mg/L. It has been used widely with good results to detect cardiovascular disease, to monitor cardiac treatment, and to predict future outcomes of cardiovascular disease. The critical range of CRP levels in patients with cardiovascular disease is 1 to 10 mg/L. The baseline level of perfectly healthy individuals, however, may be <0.15 mg/L, particularly in Asian populations.

If CRP is to be used as a marker to assess wellness of healthy individuals, the sensitivity of the current hs-CRP test needs to be improved to assay serum CRP levels <0.01 mg/L. An alternative would be to use the competitive immunoassays or immunometric assays of CRP that were developed before the hs-CRP test became widely available. Most important, the price of the test should be reduced substantially so that the general population can afford regular checkups by direct access testing. Ordering tests by patients instead of physicians seems to be a trend for the future and such testing may not be covered by health insurance [4].

**CRP Assays and Reference Ranges**

Traditionally, during the acute phase of infection, serum CRP levels were measured by rate nephelometry (“serum CRP assay”). Elevated CRP values may reach a magnitude of thousands of mg/L. These assays have a lower limit of detection of only 6 to 10 mg/L. The more sensitive latex particle-enhanced immunoturbidimetric assay (“high sensitivity [hs]-CRP assay”) has a lower limit of detection (or sensitivity) of about 0.15 mg/L. It is used to assess for cardiovascular risk. With this assay, the tertiles of cardiovascular risk factors are CRP <1 mg/L for low risk, 1 to 3 mg/L for moderate risk, and 3 to 10 mg/L for high risk. CRP levels >10 mg/L generally are considered to indicate bacterial infection and the test is repeated 2 weeks later [5].

In fact, several assays developed prior to the hs-CRP assay are even more sensitive. For example, an in-house ELISA CRP assay developed in 1997 had a sensitivity of 0.007 mg/L and was used in 1999 to evaluate the hs-CRP test for clinical use [6-8]. As early as 1981, a solid-phase single-antibody competitive radioimmunoassay with a single rabbit anti-CRP antibody directly immobilized onto magnetic particles had a sensitivity of 0.05 mg/L. With use of a double-antibody competitive radioimmunoassay, the sensitivity was increased further to 0.003 mg/L. In the double-antibody assay, rabbit anti-CRP antibody was first incubated with serum containing CRP in a liquid phase. After the liquid-phase incubation, a second antibody of goat anti-rabbit IgG immobilized on magnetic particles was added to separate free and bound fractions of the radioimmunoassay system. With this simple treatment, assay sensitivity was increased >16-fold [9].

In 2000, an immunoradiometric assay (IRMA) was developed with polyclonal antibodies of CRP immobilized on microtiter plates and monoclonal antibodies of CRP labeled with $^{125}$I. IRMA had a sensitivity of 0.05 mg/L [10]. Many clinical scientists have questioned the correctness of the term “high-sensitivity C-reactive protein (hs-CRP)” when used to present the results of CRP obtained by the hs-CRP method. This confusion needs to be avoided in the future.

To reduce reagent costs, a latex particle-enhanced immunoturbidimetric assay was developed in-house with commercially available reagents and run on automatic instruments to achieve good correlation ($r = 0.988$) with the commercial hs-CRP assay (Behring, Inc., Sommerville, NJ) [11].
The reference ranges of serum CRP levels in the Western and Asian populations are widely different. In a combined report of 4 studies that included 22,403 apparently healthy U.S. adults, the 10th, 50th, and 90th percentile values for CRP were 0.40, 1.50, and 6.05 mg/L for men and 0.29, 1.52, and 6.61 mg/L for women, respectively [8]. In a study of 6,107 apparently healthy adults in Japan, the percentile distributions were much lower than that of the U.S. population, with the 10th, 50th, and 90th percentile values being <0.03, 0.16, and 0.78 mg/L for Japanese men and <0.03, 0.09, and 0.57 mg/L for Japanese women, respectively. Thus, the serum CRP levels of the Japanese population were less than one-tenth the levels of the U.S. population [12]. In a study of 16,945 men and women in Germany, Scotland, and France, the median values were 0.6 to 1.1 mg/L for those ≤44 years old and 1.2-1.7 mg/L for those >45 years old (hs-CRP assays and solid-phase double antibody radioimmunoassay) [13]. These median values were similar to those of the U.S. population. The study also reported that during a 15-year period, the median CRP values of the European population did not change significantly [13].

According to a pilot study with an in-house immunochemiluminometric CRP assay (sensitivity, 0.004 mg/L), of 472 Chinese in Taiwan, the median CRP level of Han Chinese residing in Taiwan was about 0.04, 0.34, and 1.91 mg/L for the 10th, 50th, and 90th percentiles, respectively [14]. The differences between men and women were not significant. The ranges determined in Taiwan were one-fifth of those in the U.S. population but 2-fold higher than those in the Japanese population. Do these findings reflect genetic differences or environmental differences?

CRP and Cardiovascular Disease

CRP has become a widely used test because of close association between serum CRP levels and cardiovascular disease. Cardiovascular disease is an enormous public health problem. According to a 2002 study, it is the leading cause of death in the United States, surpassing any cancer cause of death. Cardiovascular disease generally is thought to be caused by 2 principal factors: atherosclerosis and inflammation. Inflammation may be a major and initial cause of cardiovascular disease. The Centers for Disease Control and Prevention (CDC) and the American Heart Association (AHA) workshop on markers of inflammation and cardiovascular disease reported that a serum CRP value >3 mg/L increased the risk of death or myocardial infarction 5 times compared with a value ≤3 mg/L. Cardiovascular patients with CRP levels >10 mg/L at entry had >4 times the risk of death during follow-up [5].

The CDC and AHA workshop recommended that serum CRP be used as a marker of inflammation in patients with cardiovascular disease [5]. On the basis of this report, scientists also suggested it would be valuable to use CRP as an initial screening test in conjunction with a conventional lipid test for assessing cardiovascular risk [18]. Serum CRP, however, is nonspecific, and 40% of women who are seemingly healthy and in the low-risk age range of 30 to 39 years have CRP values >3.5 mg/l [19]. Another study showed that 2,459 patients who had cardiovascular disease had a low odds ratio of CRP, 1.45 (95% CI, 1.25-1.68) [20]. Because of the poor predictive value of CRP, Levinson et al [21] concluded that the use of CRP tests for screening for cardiac diseases is not justified economically and that the use of CRP screening needs to be reassessed. However, CRP test results can be helpful when they are interpreted with other cardiovascular risk factors. As shown by Rifai and Ridker [8], if
the serum CRP level is >3 mg/L, the relative risk of coronary heart disease increases with an increase in the low-density lipoprotein of (LDL)-cholesterol level, and when LDL-cholesterol reaches 1,600 mg/L the relative risk of coronary heart disease is 8.0 [8].

An autopsy study of patients with myocardial infarction demonstrated inflammation of coronary vessels, suggesting that CRP levels may reflect the atherosclerotic process and identify the risk of future cardiovascular events. Some investigators have recommended that CRP testing be used in the primary prevention of cardiovascular disease instead of population-wide screening; however, others have indicated that the optimal use of CRP as a screening test in the general population remains to be determined [22,23]. A 10-year follow-up study of 15,632 U.S. women reported that the higher the baseline CRP level, the higher the rate of cardiovascular events [24].

Effects of Genetics and Lifestyle on Serum CRP

Lifestyle has a stronger effect than genetics on CRP. In a study of 194 healthy female twins, CRP levels differed in monozygotic twins according to their adiposities (or greater body mass). In discordant pairs of monozygotic twins, the twin with higher adiposity had a CRP level 2.5-fold greater than that of the other twin with lower adiposity [17]. This is evidence that environmental factors have a stronger influence than genetic factors on an individual’s CRP value. Also, lifestyle factors may be more important than genetic factors in accounting for the difference in CRP values between Asian and Western populations.

Physical activity overcomes estrogen to reduce CRP. Thirty-five years ago, a review of various drugs that interfere with serum protein concentrations mentioned that CRP levels were elevated in women who took oral contraceptive agents containing estrogen-progestin hormones [26]. Today, we know that postmenopausal women who take hormone replacement therapy also have elevated CRP levels. However, serum CRP levels are not elevated in physically active postmenopausal women, including those who take hormone replacement therapy [27]. This strongly indicates the benefit of physical activity over a sedentary lifestyle.

Healthy diet reduces CRP. In an Italian university hospital, 90 patients were instructed to follow a Mediterranean-style diet by increasing daily consumption of whole grains, fruit, vegetables, nuts, and olive oil [28]. Another 90 patients who served as a control group followed a prudent diet of 50% to 60% carbohydrates, 15% to 20% proteins, and <30% total fat. After consuming the Mediterranean-style diet for 2 years, the experimental group had significantly reduced serum CRP levels (from 2.8 to 1.7 mg/L, p <0.01) and body mass index (from 27.9 kg/m$^2$ to 26.7 kg/m$^2$, p <.0001). The control group did not show any significant change [28].

In a 10-year longitudinal aging study of 1,507 apparently healthy men and 832 women (age 70-90 years) from 11 European countries, those who adhered to a Mediterranean-style diet and healthy lifestyle (physical activity, moderate alcohol use, and nonsmoking) had a mortality rate >50% lower than the other subjects [29]. In the USA, the NHANES (National Health and Nutrition Examination Survey) of 3,920 participants older than 20 years showed that dietary fiber intake is associated inversely with serum CRP level, and this may be extrapolated to include a decrease in the risk of developing cardiovascular disease [30].

Bad habits increase CRP levels. In the Monitoring Trends and Determinants in Cardiovascular Disease (MONICA) Augsburg Study, the serum CRP levels of 936 men 45 to 64 years old were determined with a sensitive IRMA and the range was 0.05 to 10 mg/L. The distribution of log-CRP values was a smooth and symmetrical curve without skewness. The geometric means of the CRP values transformed back from antilog of never smoking, ex-smoker, and current smoker were 1.24, 1.37, and
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2.44 mg/L, respectively; a body mass index of <25, 25 to 30, and ≥30 kg/m² was 1.06, 1.71, and 2.11 mg/L; 8, 12, and 17 years of schooling was 1.91, 1.75, and 1.12 mg/L [31]. Smokers have higher serum CRP levels than nonsmokers; smoking is a self-controllable risk that contributes to an increase in the serum CRP level. Other risk factors such as lack of physical activity and high body mass index also increase CRP levels. A greater number of years of schooling is associated with lower CRP values (p <0.05) [31]. This strongly indicates that public health has room for further improving the health and wellness of the general population.

Effective drugs decrease CRP. If the target serum levels of both LDL-cholesterol (<70 mg/dl) and CRP (<2 mg/L) are achieved in patients with acute coronary syndromes receiving statin therapy, the cumulative rate of recurrent myocardial infarction or death from a coronary cause within 2.5 years is much lower than for those with LDL-cholesterol >70 mg/dl and CRP >2 mg/L. During statin therapy, the CRP level provides a risk assessment in addition to the lipid profile [32]. To detect the response of patients to intensive and moderate treatment with statin drugs, 3,745 patients with an acute coronary syndrome were randomly assigned to either intensive treatment with atorvastatin 80 mg/day (1,872 patients) or to moderate treatment with pravastatin 40 mg/day (1,873 patients) [32]. After 2.5 years, the median CRP level was significantly lower and the clinical outcome better for the intensive treatment group than for the moderate treatment group.

In an additional study of 502 patients with coronary artery disease, 253 were randomly assigned to intensive treatment with atorvastatin 80 mg/day and 252 to moderate treatment with pravastatin 40 mg/day [33]. After 18 months, the results were similar to those of the previous larger study, with the intensive treatment group having lower CRP levels and a better outcome than the moderate treatment group. The authors suggested that the serum CRP level should be included with the lipid profile in monitoring statin therapy. It would be better to compare intensive and moderate statin therapy with the same drug but different doses [32,33].

Xuezhikang, an extract of red yeast rice, contains monacolin K, whose chemical structure is similar to that of lovastatin, which is extracted from a fungus. In a double-blind study of 50 patients with coronary disease, 25 received xuezhikang 1,200 mg/day and 25 received placebo. After 6 weeks of treatment, the median CRP level in the xuezhikang group decreased from 2.7 to 1.3 mg/L (p <0.001) and in the placebo group, from 2.7 to 2.1 mg/L (p <0.05). In a recent short-term study (14 days) of 48 patients with stable angina, 24 were randomly assigned to receive xuezhikang 1,200 mg/day and 24 to receive 2,400 mg/day. The CRP level decreased at day 1 after therapy and the lipid profile decreased at day 14; however, no dose-dependent effect of xuezhikang was demonstrated [34,35].

Statin inhibits 3-hydroxy-3-methylglutaryl-CoA reductase by binding to the reductase that blocks the step of cholesterol biosynthesis. It is a potent drug for decreasing body cholesterol levels; however, the mechanism by which statins decrease the CRP level is not clear. Currently, it is thought that statins may also have an anti-inflammatory action by decreasing the lipid content of cell membranes, which disrupts T-cell membranes and reduces the CRP level [36].

Discussion

CRP is a nonspecific inflammatory marker. Its serum level increases with very mild chronic infection, as in aging, body insult, tissue damage, and cardiovascular disease and is markedly increased by a bacterial or fungal infection. By itself, CRP testing cannot be used to diagnose a specific disease, but it can be clinically useful when interpreted in the context of other clinical and pathologic results. CRP is similar to body temperature in that it contributes powerful clinical utility in the treatment of a patient’s disease [37].

If a future goal of laboratory professionals is to shift the medical paradigm from the diagnosis of disease to the assessment of wellness in order to reduce the cost of health care and to improve the quality of life [2], CRP may be a good instrument for measuring a person’s quality of life.
Long-term improvements in lifestyle, such as following a Mediterranean-style diet, increasing physical activity, reducing body mass index, and stopping smoking are accompanied by a decrease of serum CRP level. If laboratory professionals want to choose an objective marker to measure wellness, CRP is a good candidate because it has a long serum half-life of 19 hours and its level is unaffected by eating and sleeping. As the quality of life improves, fewer people get disease; this is the most cost-effective way to reduce medical costs. Laboratory professionals should choose an hs-CRP assay that can measure CRP levels <0.03 mg/L. Moreover, costs of CRP testing should be reasonable to allow for direct access testing, which may not be covered by health insurance or Medicare.

Of interest is that the Asian population has much lower serum CRP levels (10th percentile concentration, 0.03-0.04 mg/L, and 50th percentile, 0.09-0.31 mg/L) [12,14] than Western populations (10th percentile, 0.40 mg/L, and 50th percentile 1.50 mg/L) [8]. Thus, any CRP test used in Asia needs to be sensitive enough to measure 0.004 to 0.007 mg/L.

Aside from genetics, is there an environmental or dietary factor that explains the lower CRP level in the Asian population? Is red yeast rice an important dietary factor? It has not been studied scientifically. If it proves to be a factor, public health professionals should educate the Asian population to keep following this diet. The Mediterranean-style diet in Europe is being replaced by a fast-food culture, as are the traditional diets in Asia [38,39].

In summary, CRP is a nonspecific inflammatory marker. Like body temperature, it has great clinical utility but is too nonspecific to indicate a particular disease. It can be used to monitor the success of medical treatment, as in cardiovascular disease. It also can be used to measure the effectiveness of lifestyle changes such as following a Mediterranean-style or high fiber diet, increasing physical activity, reducing body mass index, or stopping smoking. The CRP test would be an excellent candidate to open up to patients as direct access testing to be used as an objective marker to assess improvements in health when making lifestyle modifications. By improving health and preventing disease, it might make health care more efficient and less costly.

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References


